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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/828,574	04/06/2001	Salvatore Albani	UCSD1310-1	6601

7590 08/29/2003

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EXAMINER	
NAVARRO, ALBERT MARK	
ART UNIT	PAPER NUMBER
1645	18

DATE MAILED: 08/29/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/828,574	Albani et al
Examiner	**Art Unit**
Mark Navarro	1645

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☐ Responsive to communication(s) filed on _____.

2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-24, 33, 34, 38-42, and 60-66* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-24, 33, 34, 38-42, and 60-66* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐	Notice of References Cited (PTO-892)	4) ☐	Interview Summary (PTO-413) Paper No.s)
2) ☐	Notice of Draftsperson's Patent Drawing Review (PTO-948)	5) ☐	Notice of Informal Patent Application (PTO-152)
3) ☐	Information Disclosure Statement.s (PTO-1449) Paper No.s)	6) ☐	Other:

DETAILED ACTION

Applicants amendments filed February 24, 2003 and June 13, 2003 (Paper Numbers 14 and 16, respectively) have been received and entered. Claims 25-32, 35-37 and 43-59 have been canceled, and new claims 60-66 have been added. Consequently, claims 1-24, 33-34, 38-42, and 60-66 are pending in the instant application.

Claim Rejections - 35 USC § 112

1. The rejection of claims 1-24 and 33-42 under 35 U.S.C. 112, second paragraph, as being vague and indefinite in the recitation of "substantially pure peptide" is withdrawn in view of Applicants amendment.

2. The rejection of claim 21 under 35 U.S.C. 112, second paragraph, as being vague and indefinite in the recitation of a chain of amino acids "similar size, charge and/or polarity." is withdrawn in view of Applicants amendment.

3. The rejection of claims 3-4 under 35 U.S.C. 112, second paragraph, as being vague and indefinite in the recitation of "conserved" is withdrawn in view of Applicants amendment.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. The rejection of claims 1-19, 21, 24, and 33-39 under 35 U.S.C. 102(b) as being anticipated by Thompson *et al* is maintained. Additionally, this rejection is applied to newly added claims 60-62, and 64-66.

Applicants are asserting that the claims have been amended to no longer recite a peptide having SEQ ID NO: 4, and that the basis for this rejection has been obviated.

Applicants arguments have been fully considered but are not found to be persuasive.

Applicants are again directed to Figure 1 of Thompson et al. Specifically, Figure 1B line 51 recites a peptide which meets all the structural requirements of claim 1 (i.e. SEQ ID NO: 14 flanked at either end by two amino acids). Accordingly, the disclosure of Thompson et al is deemed to anticipate the newly recited limitation of a peptide having SEQ ID NO: 14.

Thompson *et al* (WO 96/10039) disclose of polypeptide fragments for the use in prevention, diagnosis and treatment of auto-immune disease such as rheumatoid arthritis and

methods of preparing the fragments. Thompson *et al* further disclose of the production of a fragment identical to SEQ ID NO: 14 of the instant invention. (See Figure 1 and claims).

In view that Thompson *et al* disclose of a peptide which is 100% identical to the peptide as claimed, the disclosure of Thompson *et al* is deemed to anticipate the claimed invention. It is noted that Thompson *et al* do not characterize the peptide as binding to one or more MCH class II molecules, however in view that the peptide is identical to the peptide as claimed, it is deemed to be an inherent characteristic of the claimed peptide.

For reasons of record in Paper Number 12 as well as the reasons set forth above, this rejection is maintained for reasons of record.

5. The rejection of claims 1-17, 21, 24, and 33-39 under 35 U.S.C. 102(b) as being anticipated by Anderton *et al* is maintained. Additionally, this rejection is applied to newly added claims 60-62, and 64-66.

Applicants are asserting that Figure 13 of Anderton reports an amino acid alignment between three mammalian and one bacterial hsp60 proteins. No fragments of the full-length M. tuberculosis protein are reported in that figure. Applicant further assert that the peptide reported in Anderton that contains amino acid residues 256-270 of M. tuberculosis hsp65 is not identical to SEQ ID NO: 2 of the instant invention.

Applicants arguments have been fully considered but are not found to be fully persuasive.

Applicants arguments are not found to be fully persuasive in view of the disclosure of Anderton et al.

First, Applicants assert that Anderton in Figure 13 only reports an amino acid alignment between three mammalian and one bacterial hsp 60 proteins, no fragments of the full length M. tuberculosis protein are reported. However, Applicants attention is directed to claim 5 of Anderton. The claim is to a peptide comprising at least 5 amino acids which are in the same relative position as the amino acids in one of the sequences 81-100 and 241-270 of SEQ ID NO: 1. The fragment (241-270 of SEQ ID NO: 1) fully encompasses the structural requirements set forth in the claims (i.e., identical to SEQ ID NO: 2 and 14).

Anderton *et al* (WO 95/25744) disclose of peptide fragments which are useful for protection against or treatment of an inflammatory disease, including autoimmune diseases, such as diabetes, arthritic diseases, atherosclerosis, multiple sclerosis, myasthenia gravis, or inflammatory responses due to tumor or transplant rejection. Anderton *et al* further disclose of the production of a fragment identical to SEQ ID NO: 2 of the instant invention. (See Figure 13 and claims).

In view that Anderton *et al* disclose of a peptide which is 100% identical to the peptide as claimed, the disclosure of Anderton *et al* is deemed to anticipate the claimed invention. It is noted that Anderton *et al* do not characterize the peptide as binding to one or more MCH class II

molecules, however in view that the peptide is identical to the peptide as claimed, it is deemed to be an inherent characteristic of the claimed peptide.

For reasons of record in Paper Number 12 as well as the reasons set forth above, this rejection is maintained for reasons of record.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. The rejection of claims 1-24, 33-34, 38-42 under 35 U.S.C. 103(a) as being unpatentable over Anderton in view of Srivastava and Russel-Jones *et al* and Guichard *et al* is maintained. Additionally, this rejection is applied to newly added claims 60-66.

Applicants are asserting that the instant invention demonstrates unexpected results, and that the combination of references does not provide both a motivation for their combination and a reasonable expectation of success.

Applicants arguments have been fully considered but are not found to be fully persuasive.

First, Applicants assert that Example 2 of the instantly filed application, reports that a peptide made up of amino acids 256-270 of M. tuberculosis hsp65 could induce protection in a rat model of adjuvant arthritis. However, in children suffering from JIA, Applicants discovered that their T cells were not induced by the bacterial peptide, as measured by T cell proliferation and cytokine production assay. However, Applicants are presumably asserting that the unexpected results are obtained as a result of amino acids 254 and 255 of hsp65 being present, (SEQ ID NO: 2). However, Applicants are again directed to the disclosure of Anderton which specifically teaches of peptides which include the same structural requirement as set forth by SEQ ID NO: 2 of the instant invention. Consequently, the results obtained by Anderton et al will be identical to the results obtained in the instant invention.

Second, Applicants assert that the combination of references does not provide both a motivation for their combination and a reasonable expectation of success. However, Anderton

has taught that these stress peptide fragments (e.g. SEQ ID NO: 2 of the instant invention) are useful for protection against or treatment of an inflammatory disease. Anderton further set forth that the peptides stimulate T cell responses. (See page 5). Srivastava teaches of the improved results obtained by incorporating cytokines with stress proteins. Applicants specifically assert that there is nothing in Srivastava that suggests that E. coli is an intracellular pathogen, and could be combined with the teachings of Anderton. However, Applicants are directed to the teaching of Srivastava et al (column 7) which sets forth that antigens combined with cytokines potentiate a cytotoxic T cell response. Given that Anderton teaches that the disclosed peptide fragments elicit a T cell response, incorporation of a cytokine is recognized by those of skill in the art to potentiate the response. Accordingly, the combination of references provides motivation and a reasonable expectation of success.

The claims are drawn to an isolated HLA pan DR-binding peptides comprising a stress protein fragment that binds to a MHC class II molecule, wherein the fragment is up to about 30 amino acids in length and (I) comprises a core sequence flanked at either end by at least two amino acids, wherein the core sequence has an amino acid sequence selected from the group consisting of SEQ ID NO: 14, 15, 18, 19, 20, 21, 22 and 23, and wherein the fragment comprises a naturally occurring amino acid sequence, or (ii) comprises an amino acid sequence having at least about 70% sequence identity to a fragment of part (I).

The teachings of Anderton *et al* are set forth above.

Anderton *et al* do not teach of the peptide having one or more D-amino acids, covalently liked to an adjuvant, and further comprises an interferon.

Srivastava (U.S. Patent Number 6,455,503) teach of stress protein-peptide complexes containing a therapeutically effective amount of a cytokine including IL-1, IL2 etc. Srivastava further sets forth that the cytotoxic T cell response may be enhanced by the presence of the cytokine. (See column 7 and claims).

Russel-Jones *et al* (U.S. Patent Number 5,928,644) teach of covalent attachment of BSA to a peptide antigen results is a significant enhancement of the immune response. (See columns 2-3).

Guichard *et al* (Proc. Natl. Acad. Sci. USA, Vol. 91, October 1994, pp 9765-9769) teach that the used of D amino acids to replace natural L-peptides results in peptides with a higher metabolic stability, since most natural proteases cannot cleave D-amino acid residues.

Given that 1) Anderton *et al* have taught of fragments of stress proteins which are identical to the instantly claimed fragments, (i.e., SEQ ID NO: 2), and that 2) Srivastava teaches of the desirability to incorporate cytokines with stress proteins, and that 3) Russel-Jones teaches that covalent attachment of BSA to a peptide results in significant enhancement of the immune response, and that 4) Guichard *et al* has taught that incorporation of D-amino acids into a peptide results in peptides with a higher metabolic stability, it would have been prima facie obvious to one

of ordinary skill in the art at the time of the invention to have incorporated the cytokine with the stress protein as taught by Srivastava, or to the fused the antigen to BSA as taught by Russel-Jones *et al*, or to have incorporated a D-amino acid in the peptide antigen as taught by Guichard *et al*. One would have been motivated to incorporate these changes in view of the advantageous properties displayed by the combination (i.e., increase CTL response, increased immune response, and increased stability), as set forth by Srivastava and Russel-Jones *et al* and Guichard *et al*.

7. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark Navarro, whose telephone number is (703) 306-3225. The examiner can be reached on Monday - Thursday from 8:00 AM - 6:00 PM. The examiner can be reached on alternate Fridays. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Lynette Smith can be reached at (703) 308-3909.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Group 1645 by facsimile transmission. Papers should by faxed to Group 1645 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the official Gazette 1096 OG 30 (November 15, 1989). The CMI Fax Center number is (703) 308-4242.

Mark Navarro

Primary Examiner

August 28, 2003